Results: The clinical results are as follows:

Clinical Results	AVE	P/S	p
Acute procedural success	94.1%	94.7%	NS
Acute lesion success	99.1%	96.8%	0.053
Acute device success	97.8%	95.2%	NS
6-month TLR	8.4%	8.1%	NS
6-month MACE	16.1%	14.8%	NS

Results for the pre-determined angiographic subset (n = 300) are:

Angiographic Results	AVE	P/S	p
RVD	2.93 ± 5.4	2.93 ± 0.47	NS
Pre-MLD	1.02 ± 0.40	1.06 ± 0.39	NS
Post-MLD	2.65 ± 0.44	2.77 ± 0.48	< 0.05
6-month MLD	1.86 ± 0.86 (n = 101)	2.00 ± 0.68 (n = 109)	NS
6-month % DS	37 ± 19	34 ± 20	NS
6-month restenosis	24.8*	22.9	NS

*combined rate: de novo and restenotic lesions, all stent lengths

Conclusion: These results indicate no significant difference between AVE and P/S stents with respect to clinical and angiographic efficacy at 6 months. The only multivariable predictor of clinical restenosis was the post-procedural MLD.

11:45

809-6 Angiographic and Clinical Follow-up of Patients With Asymptomatic Restenosis After Coronary Stent Implantation

N. Nibler, A. Kastrati, S. Elezi, H. Walter, H. Schühlen, A. Schömig. *Deutsches Herzzentrum and 1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität, Munich, Germany*

This study was carried out to assess the natural course of asymptomatic restenosis after coronary implantation of Palmaz-Schatz stents. It evaluates the follow-up of 122 conservatively treated patients with restenosis of 50–75% six months after stent implantation. 62 of the 122 patients had a second angiographic follow-up at 12 months after stent implantation. Quantitative coronary angiography was performed immediately after the intervention, at 6 and 12 months after stent implantation.

	After stent implantation	After 6 months	After 12 months	p-value (6–12 months)
Coronary stenosis [%]	4.5 ± 12.1	59.1 ± 7.7	54.4 ± 15.7	p = 0.013
Minimal luminal diameter [MLD]	3.0 ± 0.6	1.24 ± 0.4	1.36 ± 0.5	p = 0.0047

A regression of restenosis (ΔMLD > +0.3 mm) was noted in 24 of the 62 patients, 10 patients displayed a progression (ΔMLD < −0.3 mm). Coronary angioplasty of the stented lesion was performed in 5% of the 122 patients included in the study, all later then 1 year after stent implantation. One myocardial infarction occurred 286 days, one cardiac death occurred 230 days after stent implantation. The 1-year-event free survival rate was 98.4%.

Conclusions: The data show that the majority of asymptomatic patients with restenosis have a favorable angiographic and clinical outcome. Regression of the angiographic mesures of restenosis occurs between 6 and 12 months after stent implantation in these patients.

810 New Approaches to Myocardial Preservation in Acute Myocardial Infarction

Monday, March 30, 1998, 10:30 a.m.–Noon
Georgia World Congress Center, Room 255W

10:30

810-1 Results of Intracoronary Recombinant Human Vascular Endothelial Growth Factor (rhVEGF) Administration Trial

T.D. Henry, K. Rocha-Singh, J.M. Isner, D.J. Kereiakes, F.J. Giordano, M. Simons, D.W. Losordo, R.C. Hendel, R.O. Bonow, J.M. Rothman, E.R. Borbas, E.R. McCluskey. *Hennepin County Medical Center, Minneapolis, MN, Genentech, Inc., So. San Francisco, CA, USA*

Background: Few therapeutic options currently exist for pts with severe coronary artery disease who have areas of viable but underperfused myocardium and who are not optimal candidates for PTCA or CABG. Animal models using rhVEGF have demonstrated angiogenesis leading to improvement in ischemic myocardium. This is the first human study designed to determine safety and tolerability of intracoronary rhVEGF. Inclusion criteria required stable exertional angina, a significant reversible defect by nuclear stress test study and suboptimal candidates for PTCA or CABG. Pts received two 10-minute intracoronary infusions at concentrations of 0.005, 0.017, 0.050, or 0.167 μg/kg/min with 3–4 pts per dose level. Pharmacokinetic sampling and hemodynamic monitoring were performed for 24 hrs. Nuclear perfusion imaging was performed before and at 30 and 60 days post rhVEGF. Angiograms were performed on 7 pts after 60 days.

Results: rhVEGF was safely tolerated at all doses. Minimal changes were seen at the lowest dose and decreases in systolic blood pressure increased to a maximum of 28 ± 8% (SEM) at 0.167 μg/kg/min. There was overall improvement in nuclear perfusion in 7/15 subjects by blinded comparisons of SPECT nuclear perfusion studies and improved collateralization in 5/7 who underwent followup coronary angiography.

Conclusion: rhVEGF appears well tolerated by coronary infusion at rates up to 0.050 μg/kg/min with encouraging initial clinical results. Further studies are in progress to determine the potential use of rhVEGF for human angiogenesis.

10:45

810-2 Kinetics of TNFα in Plasma and the Protective Effect of Monoclonal Antibody to TNFα in Myocardial Infarction

D. Li, L. Zhao, M. Liu, J. Zhang, J.L. Mehta. *Beijing Medical University, Beijing, China, and the University of Florida, Gainesville, Florida, USA*

Inflammation plays a critical role in the pathophysiology of acute myocardial infarction (AMI). Tumor necrosis factor-α (TNFα), a pleotropic cytokine, is an inflammatory trigger in several cell systems. To determine if myocyte cell death is associated with TNFα release in vivo, we monitored the alterations in plasma TNFα levels in 22 patients with AMI (Killip class I–II), 20 patients with AMI (Killip class III–IV), and 10 healthy controls by radioimmunoassay. Plasma TNFα levels were elevated in all patients in the early stages of AMI (mean ± SE, 1.47 ± 0.10 vs 10.82 ± 0.16ng/ml in controls, $p < 0.01$) with peak value at 4 hours after onset of chest pain. TNFα levels were consistently higher in patients with AMI (Killip class III–IV) than in patients with AMI (Killip class I–II) at 4, 8, 12 hrs after onset of chest pain ($p < 0.01$). TNFα levels fell thereafter, and were similar to the control value at 48 hrs after onset of AMI. To critically examine the role of TNFα release in determining infarct size, Sprague Dawley rats were treated with a monoclonal antibody (MAb) to TNFα (n = 12) or buffer (n = 12), and subjected to global myocardial ischemia-reperfusion. Treatment with TNFα-MAb decreased the area of necrosis (23.8 ± 4.5 vs 47.4 ± 5.3 in buffer-treated rats, $p < 0.01$), the number of circulating endothelial cells, an index of endothelial injury (11.7 ± 0.6 vs 21.3 ± 1.3/μl, $p < 0.01$) and lipid peroxidation (measured as malondialdehyde, 22.9 ± 2.1 vs 32.6 ± 4.3 nmol/ml $p < 0.01$). This study shows that a. TNFα release occurs early in the course of AMI, b. higher circulating levels of TNFα correlate with extensive cardiac dysfunction, and c. inhibition of TNFα decreases infarct size by influencing ongoing vascular endothelial injury and lipid peroxidation.

11:00

810-3 Morphine Mimics Ischemic Preconditioning in Human Myocardium During PTCA

N.P. Xenopoulos, M. Leesar, R. Bolli. *University of Louisville Medical School, Louisville, KY, USA*

Recent studies suggest that opioid receptors mediate ischemic preconditioning in experimental animals and that morphine mimics this cardioprotective effect. However, it is unknown whether morphine preconditions human myocardium. Accordingly, 16 patients (pts) were randomized to receive a 10-min intracoronary (IC) infusion of saline (controls [C], n = 8) or morphine sulfate (MS) (n = 8, 15 μ/kg). No hemodynamic changes were noted during the IC infusion of MS. Ten min after the completion of the IC infusion, pts underwent PTCA (three 2-min inflations, each separated by 5 min). The ST-segment shifts from baseline in the IC-ECG and in the surface ECG (S-ECG) were measured at the end of each inflation; X ± SEM; *P < 0.05 vs controls.

	IC-ECG (mm)		S-ECG (mm)	
	C	MS	C	MS
Inflation 1	29 ± 4	14 ± 3*	23 ± 4	9 ± 2*
Inflation 2	18 ± 3	15 ± 3	15 ± 3	11 ± 2
Inflation 3	16 ± 3	14 ± 3	12 ± 3	11 ± 2

During the first inflation, the ST-segment shift in both the IC-ECG and S-ECG was significantly attenuated in the MS group compared with controls (−51% and −60%). In controls, the ST shift was less during the second and third inflation than during the first, indicating ischemic preconditioning.

In contrast, in the MS group there was no additional decrease in ST shift during the second and third inflation compared with the first. The reduction in ST shift afforded by MS during the first inflation (−51% on IC-ECG vs first inflation in C) was equivalent to that afforded by ischemic preconditioning in controls (−44% during the third vs first inflation). In conclusion, pretreatment with MS mimics ischemic preconditioning during PTCA. To our knowledge, these results provide the first evidence that morphine preconditions human myocardium against ischemia in vivo and suggest that opioid receptors may play a role in the signaling pathways responsible for ischemic preconditioning in man. Because of its efficacy and safety, morphine could be used prophylactically to attenuate ischemia in high risk PTCA.

11:15

810-4 Brief Antecedent "preconditioning" Ischemia Accelerates Coronary Thrombolysis in the Canine Model

K. Przyklenk, *Heart Institute, Good Samaritan Hospital & USC, Los Angeles CA, USA*

Background: It is well-established that brief episodes of antecedent ischemia "preconditon" (PC) the heart and reduce infarct size caused by subsequent sustained coronary occlusion. In addition, recent studies from our laboratory revealed that brief antecedent PC ischemia also attenuates subsequent platelet aggregation in damaged and stenotic coronary arteries by an adenosine-mediated mechanism. Our current aim was to determine whether the antiplatelet properties of PC ischemia result in more rapid reperfusion and better maintenance of subsequent vessel patency in the setting of coronary thrombosis/thrombolysis.

Methods: Anesthetized dogs underwent 10 min PC ischemia + 10 min reflow (n = 7) or no intervention (n = 7) prior to initiation of thrombotic coronary artery occlusion. At 1 h after the onset of thrombosis, all dogs received 1.3 mg/kg rt-PA. Primary study endpoints included the time required to achieve reflow; the duration of spontaneous reocclusion during the 2 h after initial lysis; and the total duration of thrombotic occlusion (all with nonparametric distributions and thus reported as the median [25th; 75th] percentiles). As secondary endpoints, collateral blood flow was measured during thrombotic occlusion by injection of radiolabeled microspheres, and infarct size delineated by tetrazolium staining and expressed as a % of the myocardium at risk.

Results:

	Control	Preconditioned
Time to lysis (min)	47 [13; 50]	11 [7; 14]**
Time spent reoccluded (min)	20 [2; 52]	6 [0; 10]
Total time occluded (h)	1.9 [1.6; 2.6]	1.3 [1.1; 1.4]**

The time required to achieve initial lysis was significantly shortened, and subsequent vessel patency tended to be better maintained, in dogs that received antecedent PC ischemia vs controls (**p < 0.05). This was, not surprisingly, accompanied by a significant reduction in infarct size (11% vs 32% of the risk region; p < 0.05), despite comparable collateral perfusion, in the PC group.

Conclusions: Brief preconditioning ischemia – in addition to its well-documented cardioprotective properties – markedly shortens the time required for rt-PA-induced thrombolysis in this canine model.

11:30

810-5 In Vivo Suppression of Myocardial Apoptotic Cell Death by Insulin-like Growth Factor IGF I and II

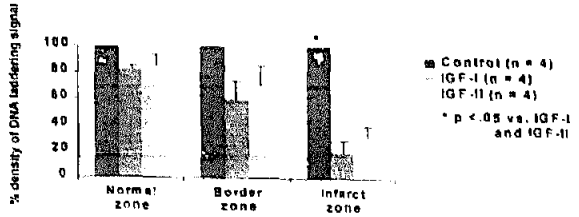
M. Scheinowitz[1], G. Sangiorgi[2], L.G. Spagnoli[3], A. Orlandi[3], A. Kotlyar[1], D. Hasdai[2]. [1]*The Neufeld Cardiac Research Institute, Tel-Aviv, Israel;* [2]*Mayo Clinic, Rochester, USA;* [3]*University of Rome Tor Vergata, Rome, Italy*

Background: Apoptosis (Apo) is a form of programmed cell death occurring in physiological and patophysiological states including myocardial infarction (MI). Insulin-like growth factors (IGF) I and II have been shown to suppress Apo in vitro, but their in vivo effects are unknown. The purpose of this study was to examine the effects of intracoronary IGF-I and II administration on myocardial Apo in acute MI.

Methods: Coronary microembolization was performed using 100μ affigel beads in pigs randomly assigned to 0.5 μg IGF-I, IGF-II, or bovine albumin, incorporated within the beads and gradually released. After sacrifice at 4 weeks, myocardial samples from the infarct (I), border (B), and normal zones (N) were assessed for Apo by TUNEL and ligation-mediated PCR.

Results: TUNEL-positive cells were observed particularly in I and B and were reduced in the treated animals. Using PCR, IGF-I and II were also found to reduce the DNA laddering signal in I, with a similar trend in B (see figure).

Conclusions: Both IGF-I and II suppressed Apo in this porcine model of acute myocardial infarction, supporting a role for IGF-I and -II in regulating myocardial Apo in vivo.



11:45

810-6 Use of a Novel Anti-Apoptotic Agent (LXR017) Reduces Infarct Size Following Ischemia-Reperfusion in the Canine Myocardium

M.J. Silver, S.P. Chetcuti, D.B. Mukherjee, J.L. Malycky, D.L. Tomei[1], S. Umansky[1], F.A. Nicolini. *The Cleveland Clinic Foundation, Cleveland, OH, USA;* [1]*LXR Biotechnology Inc. Richmond, CA, USA*

We have previously shown that a phospholipid agent (LXR017) specifically prevents apoptotic cell death induced by serum/glucose deprivation, a parallel to in-vivo ischemia reperfusion injury, in rat neonatal cardiomyocytes. Since apoptosis plays a major role in myocardial cell death following ischemia reperfusion, we sought to test the efficacy of LXR017 in an in-vivo model of ischemia reperfusion. Twenty open-chested dogs underwent temporary LAD occlusion (90 min) followed by reperfusion (3 hrs). All dogs had continuous monitoring of ECG, left ventricual pressure, and dP/dt. Fifteen min prior reperfusion, dogs were randomly administered either an intracoronary infusion of placebo (n = 6), SOD-Catalase (5 mg/kg; n = 5) a positive control group, or LXR017 (250 μg; n = 9) for a total of 75 min. Endpoints included infarct size measured by TTC staining (% of area at risk), regional shortening fraction (SF) via sonomicrometer crystals, regional myocardial blood flow via radioactive microspheres, and myeloperoxidase (MPO) activity. Baseline hemodynamics as well as regional myocardial blood flow were similar among groups and did not differ during the course of the study. Infarct size, MPO and SF findings at 3 hrs of reperfusion indicate that LXR017 protects the ischemic-reperfused canine myocardium, and may provide a valuable new adjunct to reperfusion therapy for acute myocardial infarction.

	Infarct Size (%)	MPO (U/min/g)	SF (%)
Placebo	22 ± 2	0.198 ± 0.09	3.32 ± 3.08
SOD-Catalse	11 ± 6*	0.096 ± 0.01*	2.82 ± 2.85*
LXR017	10 ± 4*	0.094 ± 0.03*	3.12 ± 2.59*

Data are presented in mean ± SD *P 0.04 vs Placebo by ANOVA

811 Dilated Cardiomyopathies: New Observations and Approaches

Monday, March 30, 1998, 2:00 p.m.–3:30 p.m.
Georgia World Congress Center, Room 367W

2:00

811-1 The Frequency of Familial Disease in a Consecutive Series of 51 Patients With Idiopathic Dilated Cardiomyopathy

A. Gavazzi, M. Ponzetta, C. Campana, M. Giraldi, C. Inserra, A. Raisaro, M.L. Laudisa, E. Colombi, B. Del Bello[1], E. Arbustini[1]. *Divisione di Cardiologia, Italy;* [1]*Istituto di Anatomia Patologica dell'Università, IRCCS Policlinico S. Matteo, Pavia, Italy*

Background: Familial disease may account for a significant proportion of patients with dilated cardiomyopathy (DCM) and could be more frequent than is often recognised. Most previous reports are of anedoctal or retrospective nature and only a few prospective studies have been published. Consequently, the real frequency of familial disease in DCM remains to be established.

Methods: Our aim was to assess the frequency and mode of inheritance of familial disease by prospectively screening relatives from a series of 51 consecutively diagnosed patients with DCM. The diagnosis of DCM was confirmed invasively in every patient. All patients had a 2–3 generation pedigree constructed. Familial disease was diagnosed when at least one relative was affected by DCM. Screening consisted of history, clinical examination with blood pressure measurement, 12 lead ECG, two dimensional Doppler echocardiography, signal averaged ECG (SAECG) and blood sample (serum CK).

MONDAY ORAL